

### **REMARKS/ARGUMENTS**

#### **35 USC §112**

With reference to paragraph 2 of the Official Action mailed on April 22, 2008, the Examiner's comments concerning the meaning of "n-alkanol" are noted, but it is respectfully submitted that these are incorrect and that an "n-alkanol" does not refer to a hydrocarbon in which the -OH group is attached only to carbon 1. Rather, the prefix "n-" or "normal-" designates hydrocarbons which contain a single unbranched chain of carbon atoms. The "n-" prefix does not describe the positioning of any of the active groups on the hydrocarbon chain, these active groups instead being named as the Examiner correctly states for -OH groups as 1-alcohols or 2-alcohols etc, also known as primary or secondary alcohols respectively.

For instance n-butan-2-ol refers to a hydrocarbon comprising a 4 carbon linear chain with a hydroxyl group on the second carbon atom.

Therefore the current patent application is in agreement with the IUPAC Nomenclature of Organic Chemistry (the "*Blue Book*") which is the International standard reference for the naming of Organic compounds. We accept that the "n-" nomenclature is an older means of describing organic compounds and so is potentially confusing.

In any event, with reference to the present patent application it is clear that the inventors mean the term "n-alkanol" to refer to compounds which can have the hydroxyl at either the first, second or other carbon atom. See for instance page 3 paragraph 0037 of this patent application as published wherein it is stated "According to an advantageous embodiment of said use, said n-alkanols are linear, ..., hydrocarbon-chain n-alkanols in which the OH group is in the 1-position (primary alcohol) or in the 2-position (secondary alcohol)". As the examiner correctly stated in the last detailed Official Action, the Applicant can act as their own lexicographer within the patent application, and in this patent application the meaning of n-alkanol without any reference to any other teaching from this field is clear. That is, that n-alkanol refers to compounds which can have the hydroxyl at either the first, second or other carbon atom.

In conclusion therefore claim 9 and claims 2 and 4-8 which are dependent thereon are clear as to the meaning of "n-alkanol".

With reference to paragraph 4 of the Official Action, claim 9 has been amended to correct the typographical error (superscript rather than subscript) noted by the Examiner.

With reference to paragraph 5, in view of our comments above it is submitted that claim 2 is of proper dependent form, because as pointed out the term “n-alkanol” of claim 9 refers to a hydrocarbon comprising a linear chain of  $C_6 - C_{10}$  comprising a hydroxyl group attached to a saturated C atom. The 1- and 2-alcohols of claim 2 are a subset of these hydrocarbons and therefore claim 2 is a dependent claim of proper form.

With reference to paragraph 7 of the Official Action, claim 9 has been amended to address the issues raised by the Examiner. Basis for these amendments can be found in the specification as originally filed and in the translation of the French priority application forwarded with our response to the previous detailed action.

In particular the term “epithelial” and specifically the use of an n-alkanol to alter the activity of CFTR in the cell membrane of epithelial cells is described as a subject of the present invention on page 9 lines 4-9 of the translation and page 3 paragraph 0033 of the patent application as published.

The term ‘patient’ and specifically the use of a n-alkanol to affect the pathology of a patient suffering a pathology related to CFTR is described on page 11 lines 21 – 32 of the translation and page 4 paragraphs 0053 and 0054 of the application as published.

The phrase “whom suffers from at least one pathology associated with the non-activation of said CFTR,” is also a stated objective of the present invention, as seen from the previously cited passages of the specification where it is stated that “The use of certain n-alkanols in the treatment of pathologies related to transmembrane chloride ion flux disorders in epithelial cells, and in particular of cystic fibrosis and of atypical cystic fibroses, have just been found by the inventors”.

Claim 9 has been amended so to more clearly specify the therapeutic target of the n-alkanols administered as part of the claimed method and also to specify the intended patients who would benefit from such therapy. This is fully supported by the specification as filed, as noted above, and is in response to the issues raised by the Examiner in paragraph 7 of the Official Action. Therefore, no new matter and no new issues are presented.

In particular, in paragraph 7 the Examiner states that new claim 9 is unclear because 'the mammal in need of' the treatment recited in this claim is not clear. As outlined above, claim 9 has been amended to specify that the method is to be performed upon a patient, limiting this claim therefore to humans. The Examiner also is concerned as to which conditions are within the scope of claim 9 and lists a number of alternative possibilities. The types of patients within the scope of this claim are those 'whom suffer from at least one pathology associated with the non-activation of said CFTR'. The effects of n-alkanol administration have been determined only insofar they relate to the activation of CFTR and it is therefore to pathologies associated with non-activation of CFTR that this claim is limited rather than to cystic fibrosis *per se* for instance. Diseases or pathologies not associated with non-activation of CFTR are not within the scope of this claim.

In paragraph 9, the Examiner states that claim 9 contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time of filing.

As pointed out above, on page 11 lines 21 – 25 of the priority document and page 4 paragraph 0053 of the application as published it is stated that "The use of certain n-alkanols in the treatment of pathologies related to transmembrane chloride ion flux disorders in epithelial cells, and in particular of cystic fibrosis and of atypical cystic fibroses, have just been found by the inventors". To paraphrase this sentence, the inventors have found in this work that n-alkanols can be used to treat certain disorders of transmembrane chloride ion channel, of which CFTR are one type and this is the subject of claim 9.

More generally and so as to place the current patent application in its proper context, we would restate that in the present application for the first time it has been shown that the administration of an n-alkanol causes the activation of CFTR in two model epithelial cell lines CHO-CFTR(+)/CHO-CFTR(-) (example 2.1) and Calu-3 (example 2.2). Administration of an n-alkanol has also been shown to cause the activation of CFTR in a primary epithelial cell culture from cystic fibrosis sufferers (example 2.3). To reiterate this important point, the administration of an n-alkanol according to the present invention has been shown to activate the endogenous CFTR in endogenous epithelial cells from several individuals whom suffer from cystic fibrosis.

In addition, the inventors also have performed the necessary further work to rule out several potential mechanisms of action for the n-alkanol, for instance n-alkanol cellular uncoupling (example 2.6) as this would have limited its usefulness as a medicament.

As stated in the present application, dysfunction of the CFTR is responsible for a number of physiopathological disorders in humans including cystic fibrosis, which is an acute condition which following several decades of intensive research still causes sufferers to have an average longevity of 30 years.

The inventors have therefore shown that the specified range of n-alkanols have a clear and specific effect upon the CFTR in both a number of known model systems as well as in the epithelial cells of a cystic fibrosis sufferer. In the present application the inventors provide a range of concentrations of the n-alkanols (page 12 lines 23 – 28 of the translation) and preferred means of administering these (page 12 lines 8 – 17 of the translation).

It is true that a final treatment regime is not provided in the present application, but it is submitted that a certain amount of undisclosed extra experimentation is inherent in putting into practice any patent which relates to the use of a substance as a medicament or for its use in a method of treating a human. Such experiments include those conducted to find the most efficacious formulation/dosage etc., and these experiments almost always occur several years after the filing of a patent and occur during or after extensive clinical trials to prove the safety/efficacy of the substance/method.

There is no reason to not believe the equivalence between the *in vitro* data provided in the current application and an *in vivo* effect and therefore such further experiments as may be necessary to actually formulate a final method of therapy based upon the administration of n-alkanols are nothing other than merely the normal pre-clinical work necessary to bring a new therapeutic method to market.

Therefore person of ordinary skill in the art, having read this patent application, would have concluded that the inventors were in possession of a method for the use of n-alkanols to treat certain specified disorders as well as the use of such n-alkanols in the preparation of medicaments for use in such methods.

In paragraph 9, the Examiner, in particular, cites four areas as lacking written support. Reconsideration by the Examiner and withdrawal of this ground of rejection are respectfully solicited in light of the following comments, which explain in detail how these claim features are supported.

(1) A method for “partially or fully” activating CFTR channels

With regard to the term “fully activating” is should be noted that at page 11, lines 26 – 32 of the translation of the French priority document it is stated that:

C<sub>6</sub>-C<sub>10</sub> n-alkanols, in particular nebulized in the bronchi of patients in the form of an aerosol or of nebulized material, activate or potentiate the activity of wild-type CFTR channels or CFTR channels that have mutated but present at the cell membrane, in particular in patients suffering from cystic fibrosis.

In the absence of any adverb associated with the word ‘activate’ which could change its meaning, this sentence is clear that the administration of C<sub>6</sub>-C<sub>10</sub> n-alkanols to a patient causes the full activation of CFTR channels therein.

With regard to the term “partially activating”, at page 24 line 15 it is stated that:

Octan-1-ol (1mM) is capable, by itself, of activating approximately 50% of the maximum activity of the mutated CFTR-ΔF508 channel (figure 10B).

Therefore in this experimental example provided in the French Priority document, it is clear that the administration of a certain quantity of a C<sub>6</sub>-C<sub>10</sub> n-alkanol, e.g. Octanol, can lead to a partial activation of mutant CFTR channels.

In conclusion therefore the full or partial activation of a CFTR by the administration of a n-alkanol are described in the French Priority document.

(2) A genus of “a mammal in need of such treatment

As explained above in connection with paragraph 7, claim 9 has been amended to specify that the method is to be performed upon a patient. This is fully supported by the priority document as noted in the discussion earlier.

(3) "Mixtures" of linear C<sub>6</sub>-C<sub>10</sub> n-alkanols

Claim 9 has been amended to delete any reference to mixtures.

(4) Administration of an n-alkanol "in an amount sufficient to generate in the vicinity of said cell membranes a concentration of said n-alkanol sufficient to partially or fully open said CFTR in said cell Membranes"

We believe this feature is fully supported by the French Priority document, in particular with reference to page 12 lines 8 – 17 of the English translation, where the means to administer n-alkanol to the surface of the bronchopulmonary mucosae is described. The bronchopulmonary mucosae comprises epithelial cells and hence this method brings the n-alkanol into contact with 'epithelial cell membranes'.

On page 12 at lines 23 – 28, a preferred range of concentration of n-alkanols is given of between 0.001% and 0.1% v/v. The inventors have gone on in the experimental examples provided, in particular at page 21 lines 2 – 5 to show that n-alkanol concentrations between 0.001% and 0.1% v/v can cause activation in two model epithelial cell lines CHO-CFTR(+)/CHO-CFTR(-) (example 2.1) and Calu-3 (example 2.2) and in a primary epithelial cell culture from cystic fibrosis sufferers (example 2.3).

Therefore the French Priority document provides basis for administering a n-alkanol so as to cause in the vicinity of epithelial cell membranes (page 21 lines 8 – 17) a concentration of the n-alkanol which is sufficient to open the CFTR in the epithelial cell membranes (page 12 at lines 23 – 28 and page 21 lines 2 – 5 as well as examples 2.1, 2.2 and 2.3).

35 USC 102 – Marcet et al.

In light of the amendments to claim 9 and the foregoing explanation, we submit that the application is entitled to the July 2, 2003 filing date of the French priority application. As such, the Marcet et al. publication is not available as prior art, and the rejection should be withdrawn.

In addition, with reference to the 35 U.S.C. 102(a) rejection of paragraph 3 of the Official Action, we must point out that the cited Marcet et al. paper, and the current patent application have three inventors in common, namely Bernard VERRIER, Brice MARCET and Patrick

DELMAS. The cited publication is, therefore, the inventors' own publication relating to the subject matter of this patent application.

By comparing the text and figures of this paper and both the translation of the Priority document and the text of this pending US patent application, it is clear that these are almost identical in their disclosure. For instance, Figure 1 of the patent application is identical to panels a-d of figure 1 of the paper, panel e from figure 1 of the paper is identical to figure 2 of the patent application and so on.

Therefore, given that the disclosures of the Marcet et al paper and the French priority patent application are essentially identical and that the current US patent application claims priority from this French patent application, Marcet et al can not be prior art for any aspect of the current US patent application.

### Conclusions

In conclusion, the clarity objections relating to the term "n-alkanol" have been overcome as the meaning of this term is consistent with the art and also unambiguously clear with respect to the specification.

As explained above, claim 9 and each of claims 2 and 4-8 have full basis in the French priority patent application as well as this US patent application as published. Therefore the Examiner's concerns regarding these claims are unfounded.

Finally, Marcet et al., is not prior art for the reasons listed above

All objections have therefore been addressed and overcome. Entry of this amendment and formal notification of the allowability of all claims as now presented are solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required

Appl. No.: 10/562,085  
Amdt. dated 07/22/2008  
Reply to Office action of April 22, 2008

therefor (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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